

**REMARKS**

**I. Status of the Claims**

Claims 1-93 were originally filed and later canceled. Claims 94-100 were added and are pending under examination. Upon entry of the present amendment, recitation of non-elected SEQ ID NOs is deleted from claims 94, 97, and 98. The amendment to the claim 1 also adds the recitation of binding to "6-n-propylthiouracil or cycloheximide," which finds support in the specification, *e.g.*, Example VII on page 91, line 17, to page 92, line 23. Claim 1 is further amended to replace "nucleic acid" with "polynucleotide" in lines 3-4 to eliminate ambiguity in antecedent basis. The additional amendment to claims 97 and 98 cures typographic errors in these claims. No new matter is introduced.

**II. Objection to the Specification**

The title of the application was objected to as being non-descriptive. The title has been amended to address this objection.

**III. Objection to the Claims**

Claims 94-100 were objected to for reciting non-elected SEQ ID NOs. All recitation of non-elected SEQ ID NOs has been deleted. The objection is thus obviated.

**VI. Claim Rejections**

**A. 35 U.S.C. §101**

Claims 94-100 were rejected under 35 U.S.C. §101 for alleged lack of a specific, substantial, and credible utility or a well established utility. Applicants respectfully traverse the rejection.

The Examiner states that "[a]pplicants have only demonstrated that the polypeptide encoded by this claimed polynucleotide is believed to be a taste receptor" (page 3, 5.A., of the Office Action mailed July 29, 2003). On the other hand, the Examiner concedes that "there is little doubt after complete characterization, this protein will probably be found to have a patentable utility" but that "this further characterization, however, is part of the art of invention

and until it has been undertaken, Applicants' claimed invention is incomplete" (page 3 of the Action). Applicants respectfully disagree with this assertion.

Applicants respectfully submit that receptors of the present invention are not "orphan receptors" as described in the Office Action. Instead, the subject application provides clear and convincing evidence that the inventors have identified a novel family of G-protein coupled receptors involved in taste transduction, *e.g.*, specific expression in taste epithelial cells, structural homology to one another, and expression in association with another taste cell specific G-protein, gustducin (*see, e.g.*, Example I on pages 82-83 describes the identification of the T2R family G-protein coupled receptors and the structural homology among the family members; Examples IV-VI on pages 85-88 describe the expression of T2R in taste receptor cells and in gustducin-expressing cells).

Furthermore, as described in Chandrashekar *et al.*, *Cell*, **100**(6): 703-711 (2000) (attached hereto as Exhibit A), it has been shown that T2Rs couple to gustducin and respond to bitter taste modulating compounds in functional expression assays. Particularly, it is disclosed therein that human T2R04 (SEQ ID NOs:7 and 8) responds to the bitter compounds denatonium and 6-n-propyl-2-thiouracil in functional assays (*see* Chandrashekar *et al.*, page 707 and Figure 5). The claimed GPCRs are not therefore merely "orphan receptors" expressed in taste cells, but are functional GPCRs that are expressed in taste cells, and that respond specifically to bitter tastant ligands.

This paper and the experimental data disclosed therein provide evidence that the subject T2Rs constitute a family of related taste receptors that respond to bitter taste stimuli. The present invention is therefore useful, *e.g.*, for screening for modulators of these taste cell specific GPCRs and for the identification of bitter taste ligands. The nucleic acids and polypeptides of the invention therefore have specific, substantial, and credible utility. Applicants therefore respectfully request that the utility rejection be withdrawn.

B. 35 U.S.C. §112, First Paragraph: Enablement

Claims 94-100 were also rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate enablement. Applicants respectfully traverse the rejection.

The Examiner first alleged that the claims are not properly enabled because the invention has neither a specific, substantial, and credible utility nor a well established utility and one of skill in the art would not know how to use the invention. As discussed above, the present invention does have sufficient utility under 35 U.S.C. §101. The enablement rejection based on lack of utility is thus inappropriate, and its withdrawal is respectfully requested.

The Examiner further alleged that even if sufficient utility exists under 35 U.S.C. §101, the specification does not fully enable the claimed invention due to the recitation of the hybridization conditions. As identified in the Patent Office and the Federal Circuit, whether undue experimentation is required by one skilled in the art to practice to invention is determined by considering factors such as the amount of guidance presented in the application, the state of the prior art, and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, a “considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede.” *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

The claims specify hybridization conditions, as well as conserved reference sequences to which the claimed nucleic acids must hybridize. Hybridization methods for the identification of nucleic acids are also well known to those of skill in molecular biology. These elements therefore provide adequate guidance for routine identification of the nucleic acids of the invention. In addition, defined functional characteristics (*e.g.*, bitter tastant ligand binding) of the proteins encoded by the claimed nucleic acids would allow one of skill in the art to identify operable embodiments and exclude inoperable embodiments. Finally, Applicants clearly meet the PTO guidelines for enablement, which set forth the standard for the scope of

enablement when a large number of possible embodiments exists. Thus, undue experimentation is not required to practice the claimed invention.

***1. The claimed reference sequences provide a meaningful structural feature that allows one of skill to identify the claimed sequences without undue experimentation***

The claims recite both functional and structural characteristics of the GPCRs encoded by the nucleic acids of the invention. The present application also provides functional assays for identification of nucleic acids encoding GPCRs of the invention, without undue experimentation. The assays and examples of the specification, together with standard methodology known to those of skill in the art, therefore provide adequate guidance for identifying nucleic acids encoding the GPCRs of the invention.

The assertion of undue experimentation appears to be based on an assumption that enablement requires the description of each and every nucleic acid that could be covered in the invention. As noted below, such a requirement is not consistent with the patent laws. Indeed, it is well settled in the biotechnology art that routine screening of even large numbers of samples is not undue experimentation when a probability of success exists. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Using the conditions set forth in the claims and specification and routine methodology, any competent laboratory technician in a molecular biology laboratory could isolate and prepare appropriate constructs, transform cells, and identify those nucleic acids that encode a GPCR of the invention with the specified binding characteristics. As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where “one of skill could readily determine any one of the claimed embodiments.” In the present case, one of skill, given the conserved amino acid and nucleotide sequences and the specified hybridization conditions, could easily screen for other nucleic acid and protein molecules that fall within the scope of the claims.

The present invention describes a family of nucleic acids encoding taste specific polypeptides which functionally are GPCRs that bind to bitter tastants, *e.g.*, 6-n-propylthiouracil or cycloheximide (as shown in Chandrashekar *et al.*, *supra*) and whose coding sequences structurally hybridize to reference nucleic acids under specified conditions.

At the time of the present invention, identification of nucleic acids having the functional and structural characteristics described above was well within the means of one of skill of the art, without undue experimentation. The present specification provides working examples and discloses standard techniques known to those of skill in the art, for the identification of functional GPCR polypeptides. One of skill in the art can use standard hybridization assays to identify nucleic acids encoding the polypeptides of the invention (*see, e.g.*, specification, pages 33-34).

Finally, functional assays to identify GPCRs of the invention are known to those of skill in the art and disclosed in the specification. For example, the specification describes methods of expressing GPCRs in heterologous cells, by coupling them to promiscuous G-proteins and then observing increases in intracellular calcium in response to ligand application (*see, e.g.*, page 59, lines 16-24). Additional assays are described in the specification, such as immunoassays (*see, e.g.*, page 59, lines 25-31), phosphatidyl inositol hydrolysis (*see, e.g.*, page 59, line 32 to page 60, lines 8), changes in cytoplasmic  $Ca^{2+}$  levels (*see, e.g.*, page 58, lines 25-32), and ligand binding assays (*see, e.g.*, page 54, line 34 to page 55, line 1). Other assays are well known to those of skill in the art.

It would not require undue experimentation to practice the full scope of the invention given the relatively small size of the genus of receptors encompassed the claims, especially because it has been established that different members of the T2R family predictably respond to different bitter compounds in functional assays, as described above. Based on the ligand binding and functional results described in Chandrashekar *et al.*, it would be routine for the skilled artisan to screen different candidate polypeptides to identify those that bind to 6-n-propylthiouracil or cycloheximide.

The assays described in the specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that screening for nucleic acids encoding GPCRs having the structural and functional characteristics described above is routine. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants therefore respectfully request that the rejection be withdrawn.

**2. One of skill in the art could readily determine any one of the claimed nucleic acids**

Finally, regarding the issue of enablement for nucleic acids, where a large number of possible embodiments exist, the PTO has provided express guidelines for examination. As set forth in the MPEP § 2164.08, a rejection of such claims such as those in the present application for undue breadth is inappropriate where one of skill could readily determine any one of the claimed embodiments.

This standard is further explained in the “Training Materials for Examining Patent Applications with respect to 35 U.S.C. § 112, first paragraph – Enablement Chemical/Biotechnological Applications,” section III.A.2.b.i(c). In the guidelines, the PTO specifically answers the question regarding scope of a nucleic acid composition claim (*e.g.*, in the present case, a nucleic acid encoding taste cell specific GPCR) left open by the Federal Circuit in *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). The claims at issue in *Deuel* were directed to any DNA encoding a specific amino acid sequence. Thus, a great number of nucleic acids were within the scope of the claims. In fact, the number was so great that a listing of all possible DNAs encoding the protein was a practical impossibility.

In the guidelines, the PTO addressed this issue, explaining that “even though a listing of all possible DNAs which encode a given protein is a practical impossibility due to the enormous number of such nucleic acids, any particular sequence can be written by one of skill given the disclosure and the sequence can be ordered from a company which synthesizes DNA.” In this manner, one of skill in the art can readily determine any one of the embodiments. The PTO concluded that scope rejections such as the one hypothesized in *Deuel* should not be advanced.

In the present application, one of skill in the art only has to identify nucleic acids that hybridize under specified conditions to conserved reference nucleotide sequences, using techniques described in the specification or known to those of skill in the art. Although many such nucleic acids are possible, one of skill can readily determine, one by one, any particular

GPCR encoding nucleic acid, without undue experimentation. For example, nucleic acid screening, hybridization, and PCR techniques are described in the specification and the art, as described above. Furthermore, one of skill can use the assays described above to test the functionality of the protein encoded by the nucleic acid of interest and easily determine if it falls within the scope of the claims. Thus, in the present application the skilled artisan can readily, with only routine experimentation, make and test any particular inward rectifier encoding nucleic acid.

The specification, combined with the state of the prior art, thus provides a number of different assays demonstrating that any experimentation required to identify nucleic acids encoding GPCR proteins is not undue. *In re Wands*, 8 USPQ 1400 (Fed. Cir. 1988). Applicants respectfully request that the enablement rejection be withdrawn.

C. 35 U.S.C. §112, First Paragraph: Written Description

Claims 94-100 were further rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description. The Examiner alleged that the claims contain subject matter insufficiently described as to reasonably convey to one of skill in the art that Applicants had possession of the claimed invention at the time of filing. Applicants respectfully traverse the rejection.

Possession of claimed invention may be shown by a variety of descriptive means, including words, structure, figures, diagrams, and formulas. MPEP §2163 I. Case law provides more specific guidance in setting the standard for written description.

Pending claims 94-100 are directed to nucleic acids encoding GPCRs that can bind to 6-n-propylthiouracil or cycloheximide. The claimed nucleic acids further hybridize to a reference polynucleotide sequence under specified conditions. These claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, “[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . .” *Lilly*, 43 USPQ2d at

1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description “requires a precise definition, such as by structure, formula, chemical name, or physical properties.” *Fiers*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

On the other hand, proper description of functional features of a claimed invention can play an important role in satisfying the written description requirement. The Federal Circuit recently stated that “*Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.” *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

With regard to the claimed nucleic acids, pending claims set forth both functional features, *e.g.*, encoding a GPCR capable of binding 6-n-propylthiouracil or cycloheximide, and structural features, *e.g.*, capable of hybridizing to a reference polynucleotide sequence under specified hybridization conditions.

The ability for a nucleic acid to hybridize under given conditions to a reference polynucleotide sequence, is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule. *See, e.g.*, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, pages 9.47-9.51 (2nd ed. 1989), attached as Exhibit B; Stryer, *Biochemistry*, pages 80-82 (3rd ed. 1988), attached as Exhibit C. As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*). Thus, pending claims set forth commonly shared structural features of the claimed nucleic acids.

Commonly shared functional features of the claimed nucleic acids are also provided: each encodes a G-protein coupled receptor capable of binding 6-n-propylthiouracil or cycloheximide. These functional features can be readily tested by one of ordinary skill in the art



using well established, routinely practiced techniques as well as according to the teaching of the present specification.

Thus, both structural and functional features commonly shared by the claimed genus have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Such description is consistent with the standards set forth in both *Lilly* and *Amgen*.

Applicants believe the claimed invention within the current claim scope is properly described by the specification under 35 U.S.C. §112 first paragraph. As such, the withdrawal of written description rejection is respectfully requested.

D. 35 U.S.C. §112, Second Paragraph

Claims 95-100 were in addition rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the Examiner asserted that the term "G-protein receptor coupled activity" in claim 95 does not have clear metes and bounds, and that the claim fails to further limit the claim scope of claim 94, from which claim 95 depends.

The indefiniteness rejection based on "G-protein coupled receptor activity" is respectfully traversed on the ground that the disclosure identifies an array of different assays for assaying the GPCR function of T2Rs according to the invention. In fact, many of these assays are classical examples of *in vitro* methods for evaluating the function of GPCRs. Furthermore, the phrase "G-protein coupled receptor activity" is defined in the specification on page 24, lines 19-26. The term "G-protein coupled receptor activity" thus does not lack clear metes and bounds.

In response to the Examiner's assertion that claim 95, reciting "the receptor ... has G-protein coupled receptor activity," does not further limit claim scope of claim 94, Applicants note that claim 94 recites the functional element of binding to 6-n-propylthiouracil or cycloheximide, which requires the binding to one of the two tastants and is distinct in scope from

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having "G-protein coupled receptor activity." Claim 95 therefore does further limit the claim scope of claim 94 by specifying an additional functional element.

The Examiner further asserted that claims 95-100 are indefinite for reciting the "nucleic acid of claim 94" when there are two "nucleic acid"s in claim 94. As amended, claim 94 now recites only one "nucleic acid" and the indefiniteness rejection is obviated.

As such, Applicants submit that the indefiniteness rejection should be properly withdrawn.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200. /

Respectfully submitted,



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Attachment (Chandrashekar *et al.*, *Cell*, 100(6): 703-711 (2000), as Exhibit A)  
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